

## REMARKS

Reconsideration of this application, as amended, is respectfully requested.

The §112 rejection is not believed to apply to the presently pending claims.

The newly presented claims are directed to a process for controlled release of liposome contents from a thermolabile liposome. Thus, the §102(b) rejection based on DE 196 22 224 ("DE '224"), which does not describe such a process, should be withdrawn.

Claims 9-13 and 15-18 were rejected under 35 U.S.C. §103(a) over WO 99/52505 in view of DE 196 22 224 or Maruyama. Claims 9-13 and 15-18 were rejected under 35 U.S.C. §103(a) over JP 05 194 92 ("JP '492") in view of DE '224 or Maruyama. Claims 13-14 were rejected under 35 U.S.C. §103(a) over JP '492 in view of either DE '224 or Maruyama, in further view of Aneja. Applicants respectfully traverse each of these rejections.

These 35 U.S.C. §103(a) rejections are all based in part on DE '224, and should be withdrawn for reasons set forth above.

Furthermore, the presently claimed invention relates to liposomes containing more than 15 to 70 wt.-% of phosphatidyl-oligoglycerol and a phosphatidylcholine with a main transition temperature in the range of from 0 to 80°C, which have been found to be surprisingly stable in solution. In contrast thereto, aggregates, which contain phosphatidylmonoglycerol (that is not according to the invention), sediment and do not form any liposomes in a solution.

Furthermore, a rapid release of the active agent is achieved by a change in temperature due to a high content of phosphatidyl-oligoglycerol.

According to the presently pending claims, a method is provided, wherein stable liposomes (i.e., at, for example, 37°C) rapidly release their content by a small temperature increase (e.g., to 40°C). Such liposomes are excellent for use in hyperthermic methods.

Further, submitted with the IDS an article co-authored by inventors Hansjörg Eibl and Lars Lindner As can be clearly gathered from Figure 5, the release of the active substance is effected promptly at a relatively low temperature increase from 39°C (empty triangles) to 40°C (gray-highlighted rectangles); more than 95% of the active substance is released in a few seconds. Thus, according to the previously claimed method, an explosion-like release can be achieved by a small increase in temperature at the tumor site. Such a method is neither taught nor suggested by the cited references.

At the time of the present invention, a skilled artisan would have to assume, based on his knowledge of the prior art, that lipid aggregates with high negative surface loadings lead to instability. Surprisingly, liposomes containing phosphatidyl-oligoglycerols behave differently, and liposome solutions are in fact obtained.

Further, a rapid release is achieved therein in a few seconds by a high content of phosphatidyl-oligoglycerol, especially with a content of more than 15%, i.e., an almost complete release of > 95% of the liposome components. In contrast, thermal releases are observed with lower contents of phosphatidyl-oligoglycerols, which, however, are usually not complete and which require a considerably longer period of several minutes.

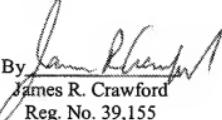
In view of the foregoing, all rejections should be withdrawn.

Allowance is respectfully requested.

The Commissioner is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 50-0624, under Order No. HUBR-1279-US.

Respectfully submitted

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